

10/522,303

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FILE COVERS 1907 - 13 May 2008 VOL 148 ISS 20

FILE LAST UPDATED: 12 May 2008 (20080512/ED)

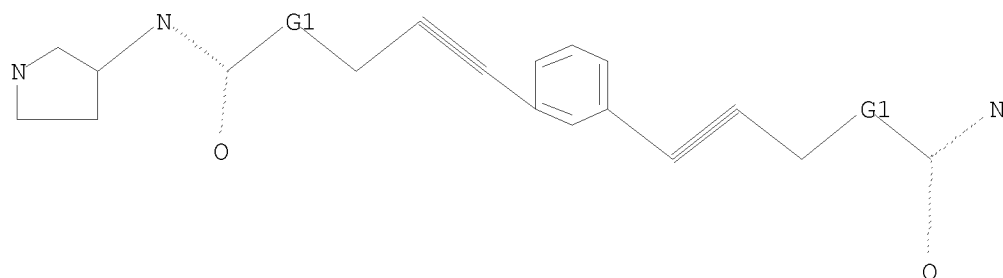
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Structure attributes must be viewed using STN Express query preparation.

L3 18 SEA FILE=REGISTRY SSS FUL L1

L4 1 SEA FILE=CAPLUS L3

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L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:120718 CAPLUS

DOCUMENT NUMBER: 140:164232

TITLE: Preparation of pyrrolidine derivatives as tryptase inhibitors

INVENTOR(S): Martin, Thomas; Ulrich, Wolf-Ruediger

PATENT ASSIGNEE(S): Altana Pharma AG, Germany

SOURCE: PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004012731	A1	20040212	WO 2003-EP8127	20030724
W: AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, US, VN, YU, ZA, ZW				
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
CA 2492830	A1	20040212	CA 2003-2492830	20030724
AU 2003250162	A1	20040223	AU 2003-250162	20030724
EP 1534267	A1	20050601	EP 2003-766278	20030724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005535685	T	20051124	JP 2004-525300	20030724
US 20050256171	A1	20051117	US 2005-522303	20050125
PRIORITY APPLN. INFO.:			EP 2002-16683	A 20020726
			WO 2003-EP8127	W 20030724
OTHER SOURCE(S):		MARPAT 140:164232		
GI				

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. I [X = -CH=C-, -CH=N-, S, or O; R1 = hydroxycarbonyl or alkoxy carbonyl; B1, B2 = O, NH, -O(CH₂)_mO-, -O(CH₂)_mNH-, where m = 1-4; K1 = -B3-Z1-B5-X1-; K2 = -B4-Z2-B6-X2-; B3, B4, B5, B6 = a bond or C1-C2 alkylene; X1, X2 = amino, aminocarbonyl, amidino, or guanidino; Z1, Z2 = 2,5-pyridinylene, 3,6-pyridinylene, 2,4-pyridinylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene, or 1,4-cyclohexylene; R2 = C(O)OR3 or C(O)N(R4)R5, where R3 = H, alkyl, cycloalkyl, cycloalkylmethyl, or benzyl, R4, R5 = H, alkyl, cycloalkyl, cycloalkylmethyl or N(R4)R5 = 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 1-piperazinyl, or 4-morpholinyl; Y = -OCH₂-, -CH₂O- or absent] were prepared as tryptase inhibitors. Thus, reaction of Me [3-{3-[3-(tert-butoxycarbonylaminomethyl)benzylaminocarbonyloxy]prop-1-ynyl}-5-(3-hydroxyprop-1-ynyl)phenyl]acetate (preparation given) with N,N-carbonyldiimidazole and Me 4-amino-1-{3-[3-(tert-butoxycarbonylaminomethyl)phenyl]propanoyl}pyrrolidine-2-carboxylate (preparation given) followed by acid hydrolysis gave compound II. The latter inhibited human tryptase with pK_{lapp} = 8.62.

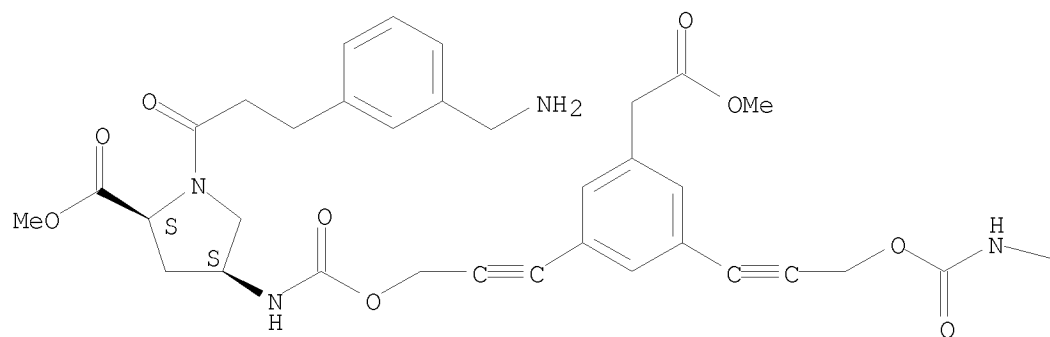
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654677-54-0P 654677-61-9P 654677-65-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolidine derivs. as tryptase inhibitors)

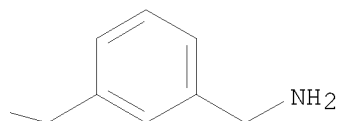
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CN L-Proline, 4-[[[3-[3-[3-[[[3-(aminomethyl)phenyl]methyl]amino]carbonyl]oxy]-1-propynyl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propynyl]oxy]carbonyl]amino]-1-[3-[3-(aminomethyl)phenyl]-1-oxopropyl]-, methyl ester, dihydrochloride, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



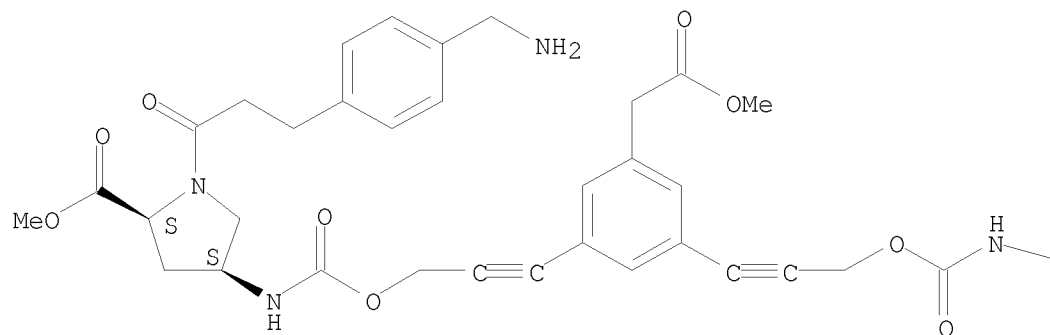
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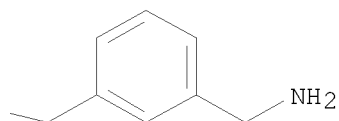
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CN L-Proline, 4-[[[3-[3-[3-[[[3-(aminomethyl)phenyl]methyl]amino]carbonyl]oxy]-1-propynyl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propynyl]oxy]carbonyl]amino]-1-[3-[4-(aminomethyl)phenyl]-1-oxopropyl]-, methyl ester, dihydrochloride, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



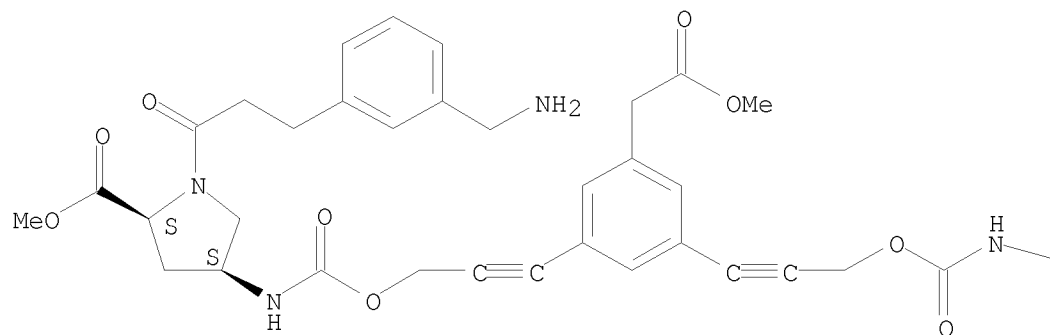
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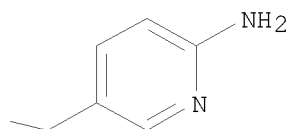
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CN L-Proline, 1-[3-[3-(aminomethyl)phenyl]-1-oxopropyl]-4-[[[3-[3-[3-[[[(6-amino-3-pyridinyl)methyl]amino]carbonyl]oxy]-1-propynyl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propynyl]oxy]carbonyl]amino]-, methyl ester, dihydrochloride, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



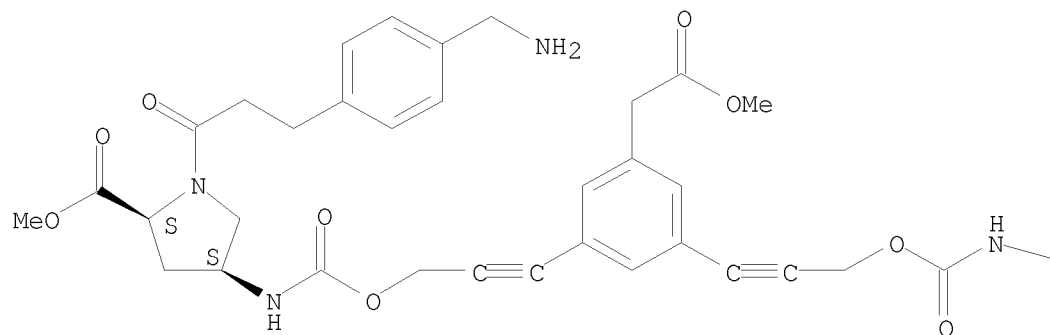
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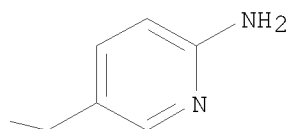
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Absolute stereochemistry.



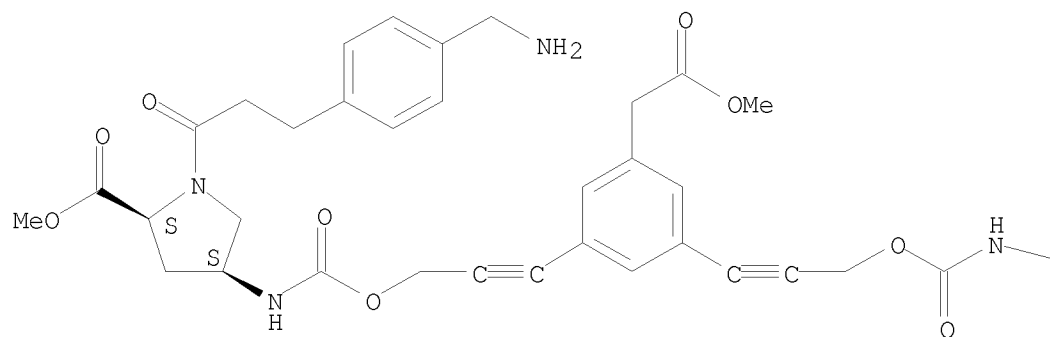
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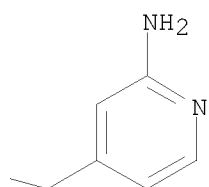
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Absolute stereochemistry.



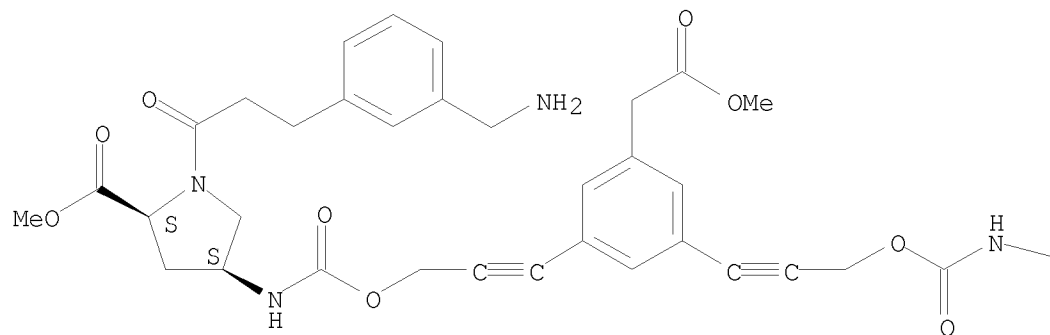
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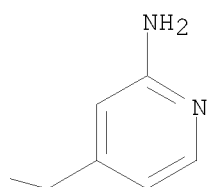
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CN L-Proline, 1-[3-[3-(aminomethyl)phenyl]-1-oxopropyl]-4-[[[3-[3-[3-[[[(2-amino-4-pyridinyl)methyl]amino]carbonyl]oxy]-1-propynyl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propynyl]oxy]carbonyl]amino]-, methyl ester, dihydrochloride, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



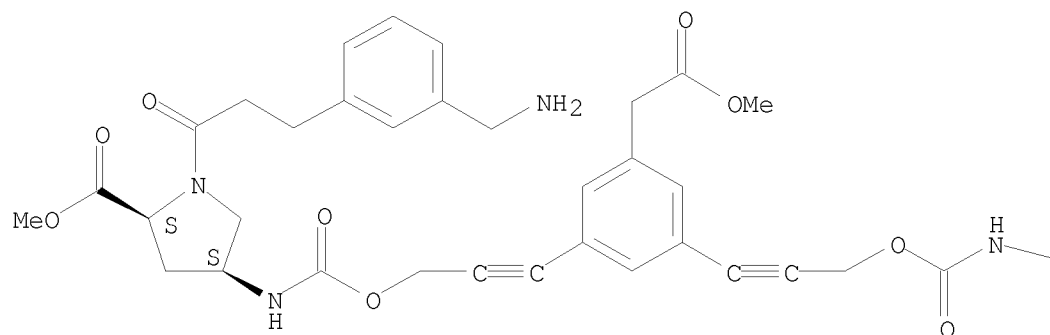
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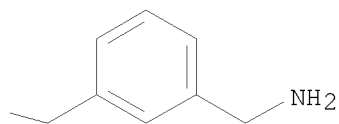


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CN L-Proline, 4-[[[3-[3-[3-[[[3-(aminomethyl)phenyl]methyl]amino]carbonyl]oxy]-1-propyn-1-yl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propyn-1-yl]oxy]carbonyl]amino]-1-[3-[3-(aminomethyl)phenyl]-1-oxopropyl]-, methyl ester, (4S)- (CA INDEX NAME)

Absolute stereochemistry.

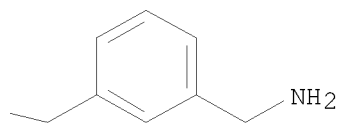
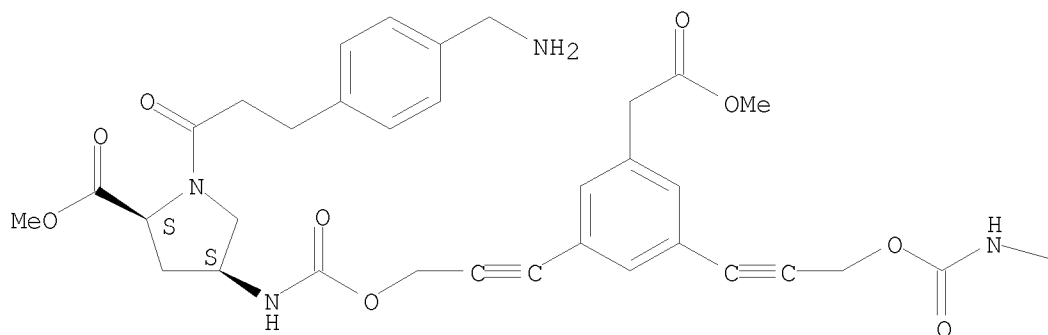




RN 654677-43-7 CAPLUS

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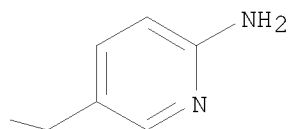
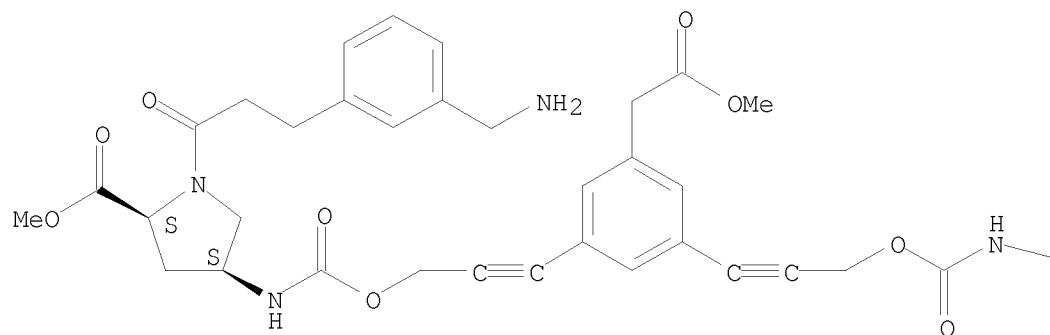
Absolute stereochemistry.



RN 654677-48-2 CAPLUS

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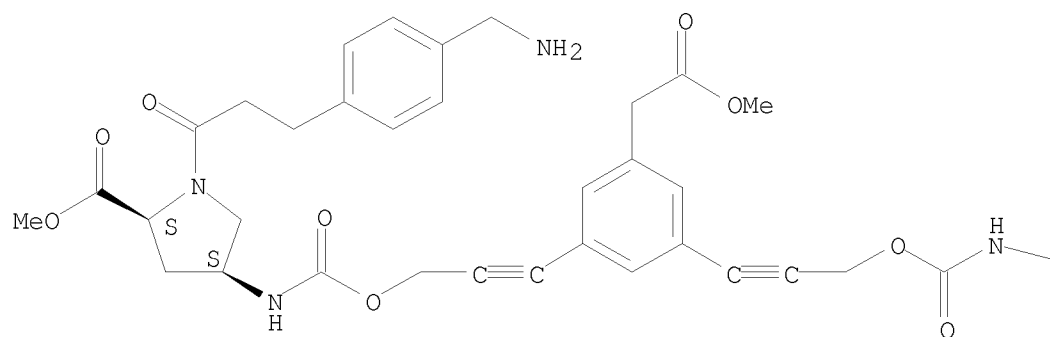
Absolute stereochemistry.

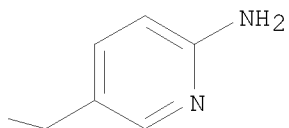


RN 654677-54-0 CAPLUS

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Absolute stereochemistry.

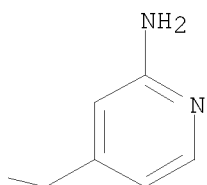
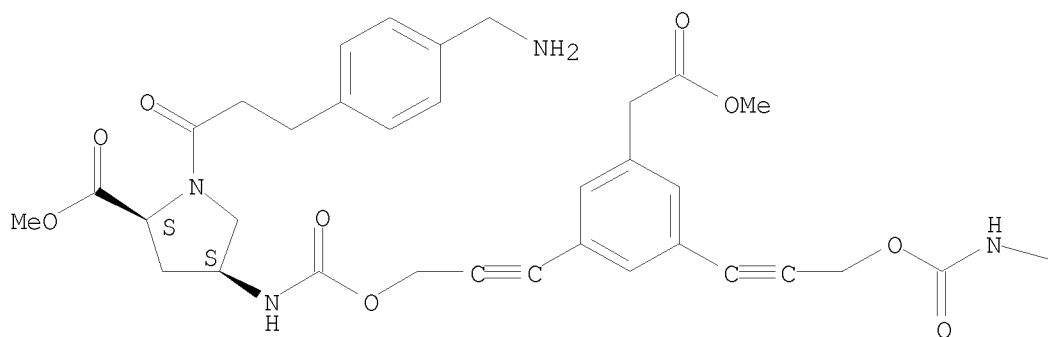




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CN L-Proline, 1-[3-[4-(aminomethyl)phenyl]-1-oxopropyl]-4-[[[3-[3-[3-[[[(2-amino-4-pyridinyl)methyl]amino]carbonyl]oxy]-1-propyn-1-yl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propyn-1-yl]oxy]carbonyl]amino]-, methyl ester, (4S)-
(CA INDEX NAME)

Absolute stereochemistry.

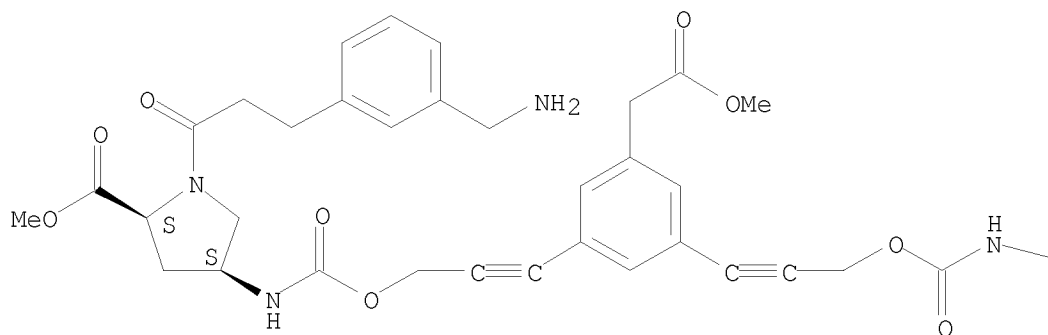


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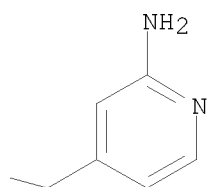
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(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



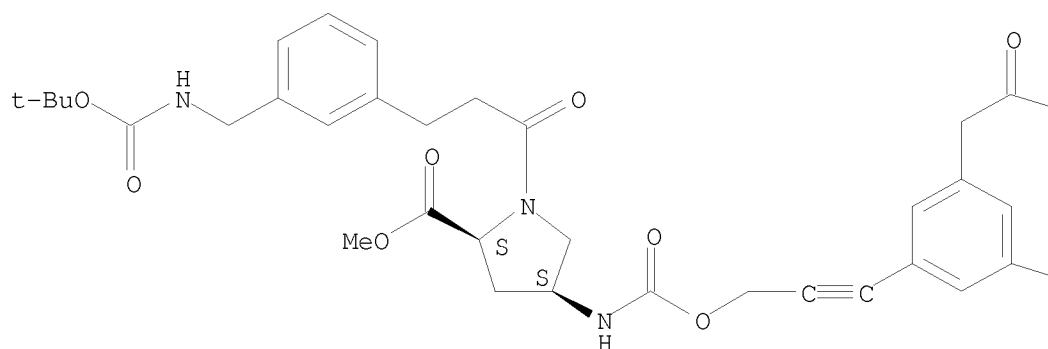
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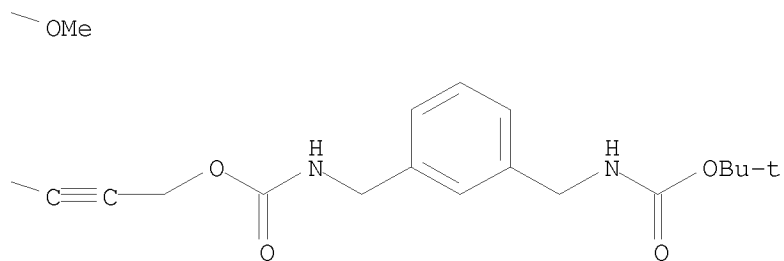


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 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of pyrrolidine derivs. as tryptase inhibitors)
 RN 654677-69-7 CAPLUS
 CN L-Proline, 4-[[[3-[3-[3-[[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]meth
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 oxoethyl)phenyl]-2-propyn-1-yl]oxy]carbonyl]amino]-1-[3-[3-[[[(1,1-
 dimethylethoxy)carbonyl]amino]methyl]phenyl]-1-oxopropyl]-, methyl ester,
 (4S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

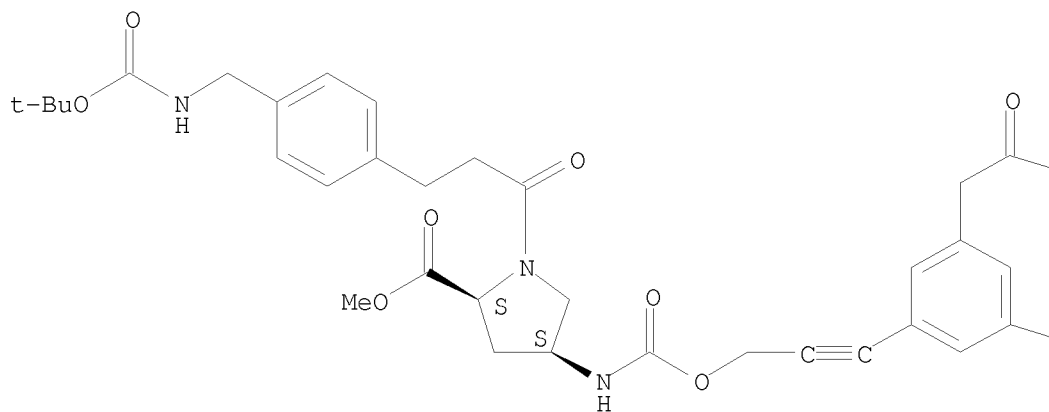


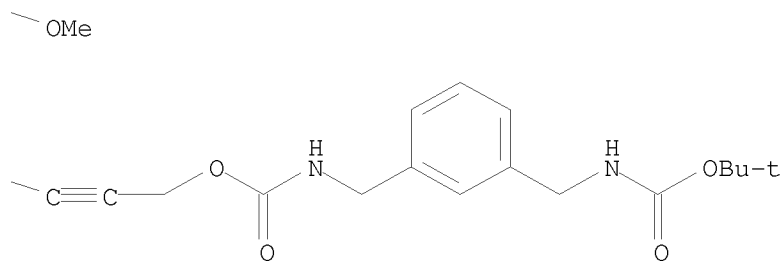


RN 654677-73-3 CAPLUS

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Absolute stereochemistry.

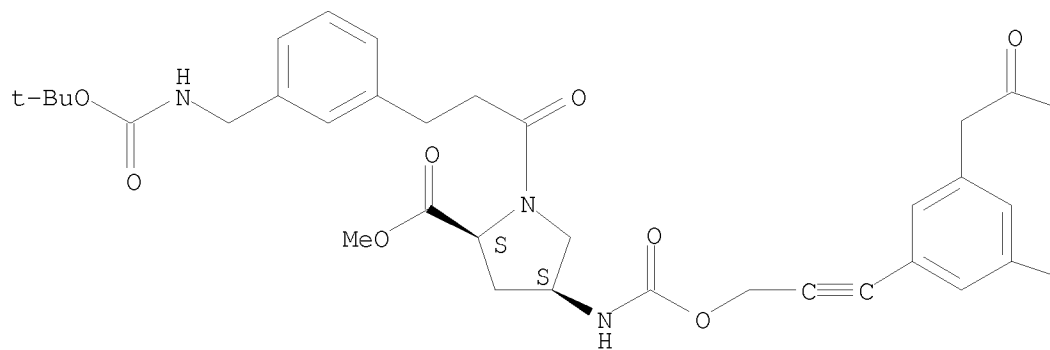


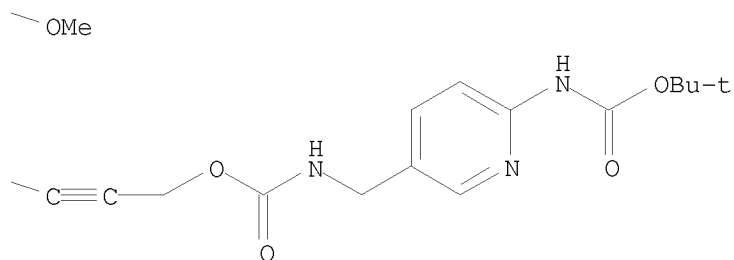


RN 654677-80-2 CAPLUS

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Absolute stereochemistry.

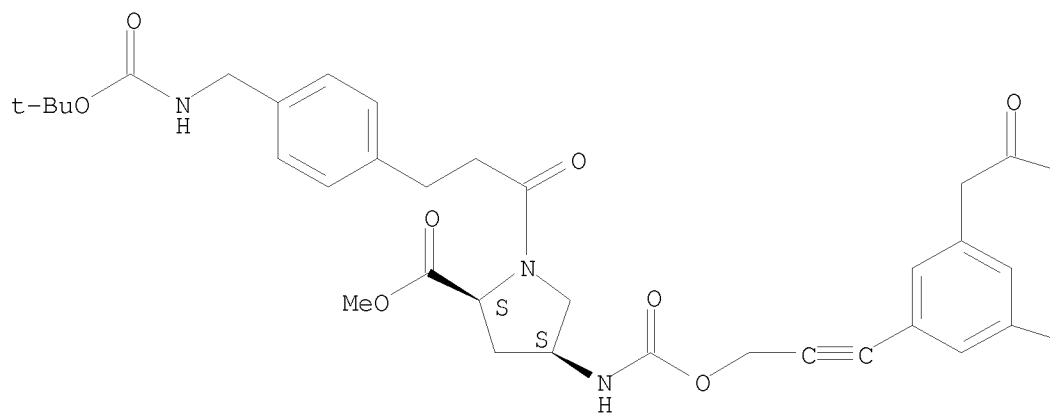


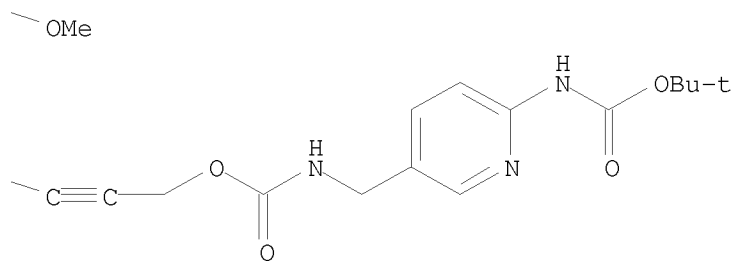


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Absolute stereochemistry.

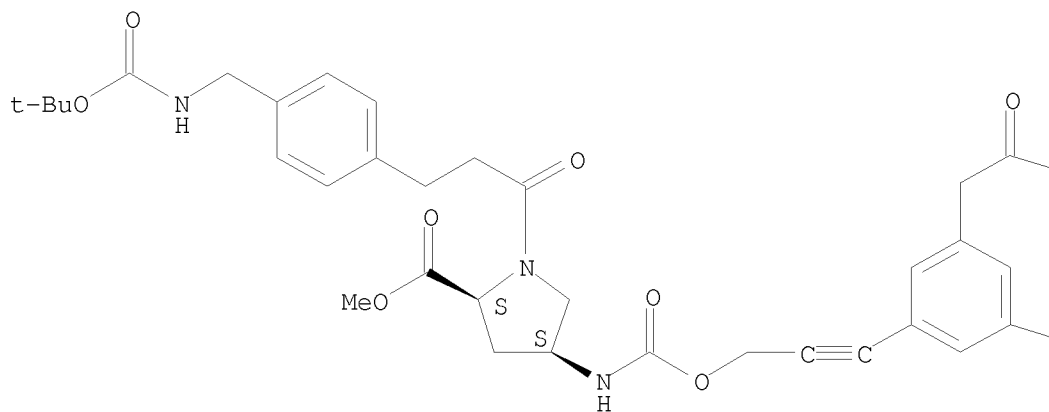


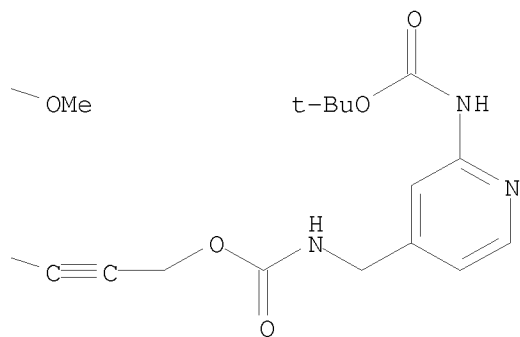


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Absolute stereochemistry.

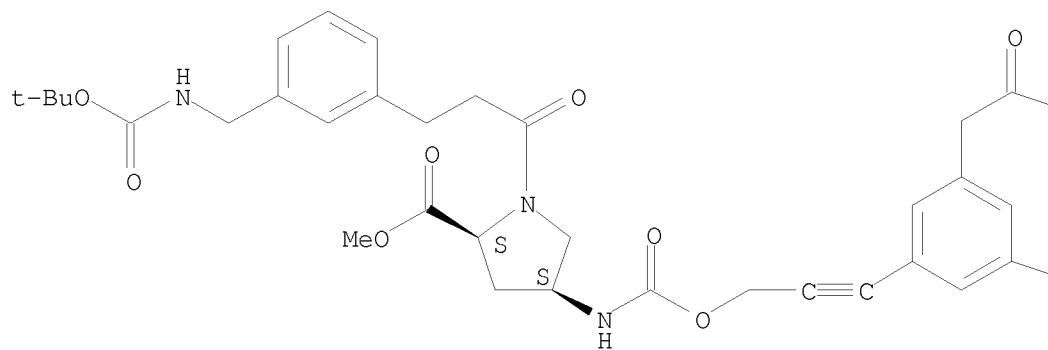




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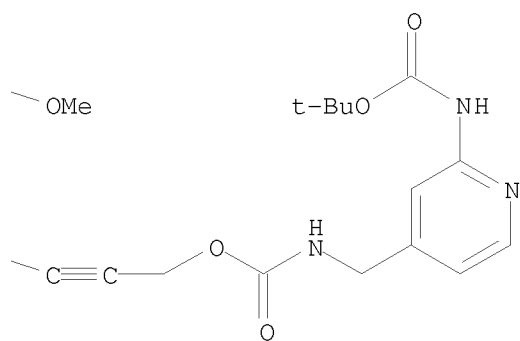
CN L-Proline, 1-[3-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]phenyl]-1-oxopropyl]-4-[[[3-[3-[3-[[[2-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-pyridinyl]methyl]amino]carbonyl]oxy]-1-propyn-1-yl]-5-(2-methoxy-2-oxoethyl)phenyl]-2-propyn-1-yl]oxy]carbonyl]amino]-, methyl ester, (4S)-(CA INDEX NAME)

Absolute stereochemistry.



10/522,303

PAGE 1-B



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